Armed Forces College of Medicine

AFCM

Cardiac Contractility

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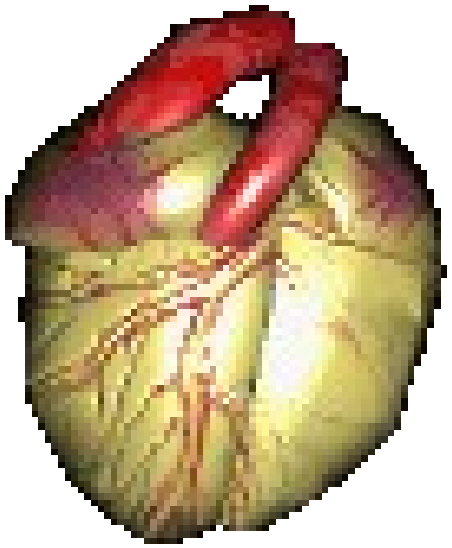


Cardiac Properties:

- ***Automaticity***
- ***Rhythmicity***
- ***Conductivity***
- ***Excitability***
- ***Contractility***

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Explain the **functional similarities and differences** between skeletal and cardiac muscle.
2. Describe the **excitation-contraction coupling** of the cardiac muscle.
3. Explain the different **factors affecting contraction** (preload, afterload, heart rate, nervous; sympathetic and parasympathetic and chemicals; neurotransmitters, hormones, ions and drugs).
4. Apply the information studied in this section to solve a clinical problem or explain a cardiac muscle contractile response.

Lecture Plan

1. Part 1 (5 min) **Introduction** to **cardiac muscle functional adaptation**

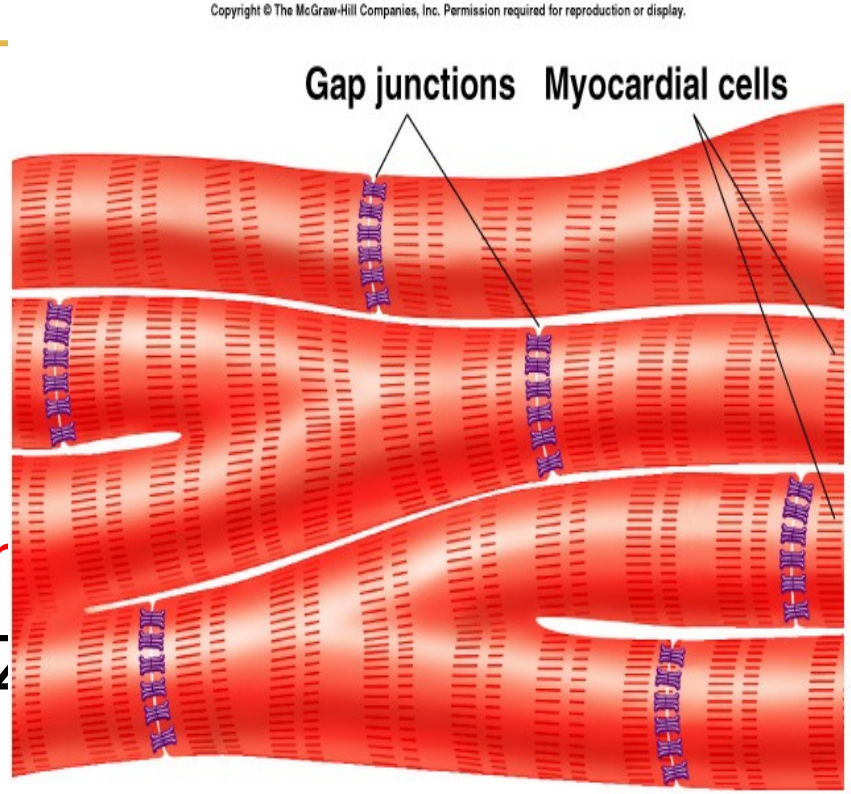
2. Part 2 (35 min) **Main lecture:**
   1. **Excitation-contraction coupling**
   2. **Factors affecting cardiac contractility**

3. Part 3 (5 min) **Summary**

4. **Lecture Quiz** (5 min)

Functional similarities and differences between skeletal and cardiac muscle

- Striated
- Z- lines, Sarcomere
- Myofilaments
- Short branched cells
- Intercalated discs
- Large number of elongated mitochor
- T-tubules more developed and over Z
- SR less developed



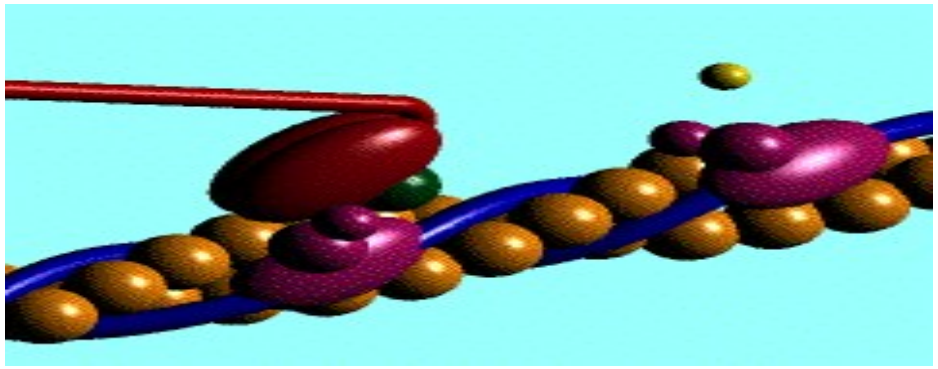
The cardiac muscle is not a true syncytium.

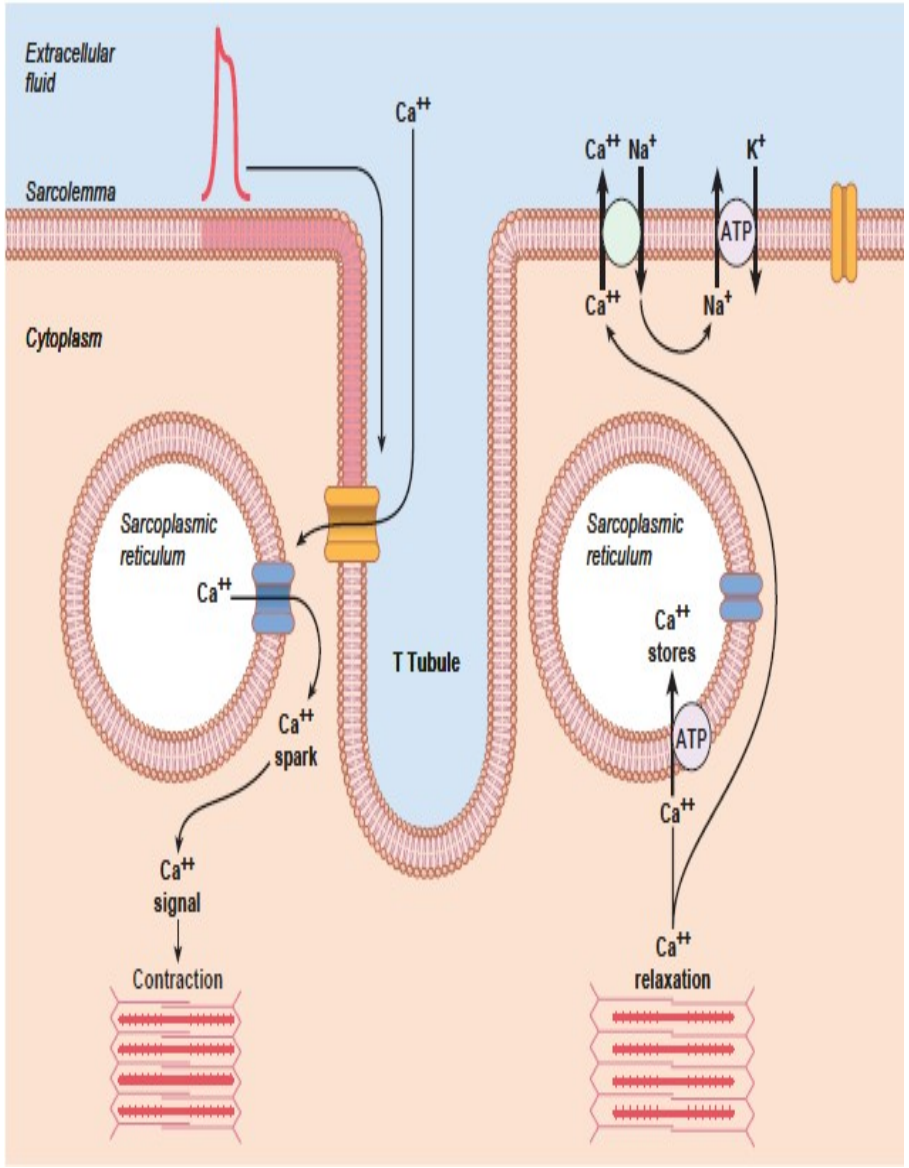
However, it acts as a functional syncytium.

Excitation-Contraction Coupling

1) Spread of excitation wave.
2) Activation of **DHP** receptors.
3) Entry of the ECF Ca^{++}.
4) Triggers CICR from SR via **RyR.**
5) Ca^{++} binds to troponin C subunit Conformational changes in the troponin-tropomyosin complex Tropomyosin moves laterally, exposing the myosin binding sites on the actin molecules Cross linkages between actin and myosin.
6) Cross bridge cycles (binding, bending, and detachment).

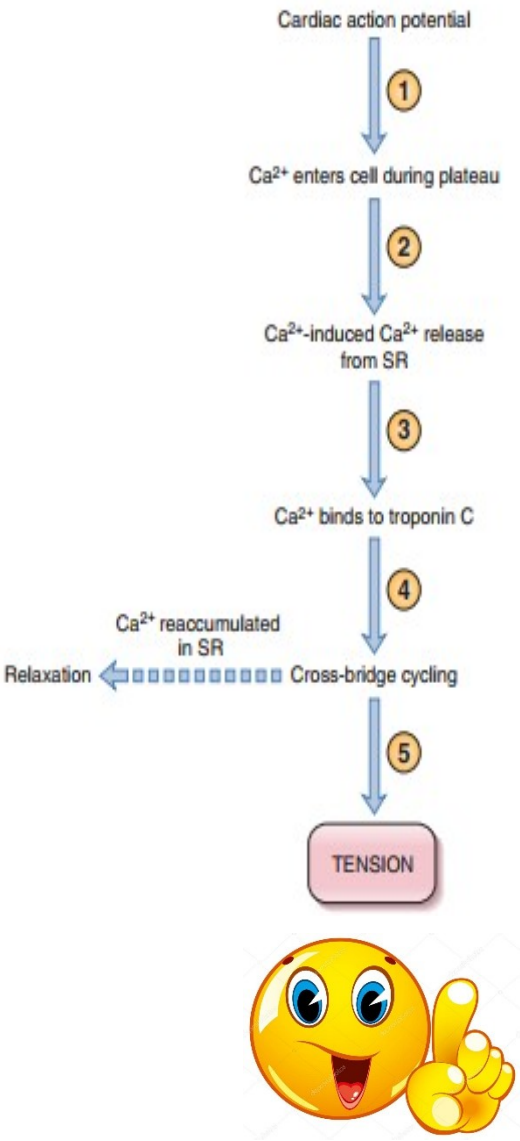
Ca^{++} Induced-Ca^{++} release (CICR)





Excitation-Contraction Coupling

- A unique feature of the cardiac action potential is its **plateau**, which results from an **inward Ca^{2+} current** through **L-type Ca^{2+} channels** (**dihydropyridine=DHP receptors**) from extracellular fluid (ECF) to intracellular fluid (ICF).
- The Ca^{2+} that enters during the plateau of the action potential is called the **trigger Ca^{2+}**.



Two factors determine how much Ca^{2+} is released from the sarcoplasmic reticulum in this step:

1. The amount of Ca^{2+} previously stored.
2. The size of the inward Ca^{2+} current (trigger Ca^{2+}) during the plateau of the action potential.

Excitation-Contraction Coupling

- Cross-bridge cycling continues as long as intracellular Ca^{2+} concentration is high enough to occupy the Ca^{2+}-binding sites on troponin C.
- The magnitude of the tension developed by myocardial cells is proportional to the intracellular Ca^{2+} concentration.

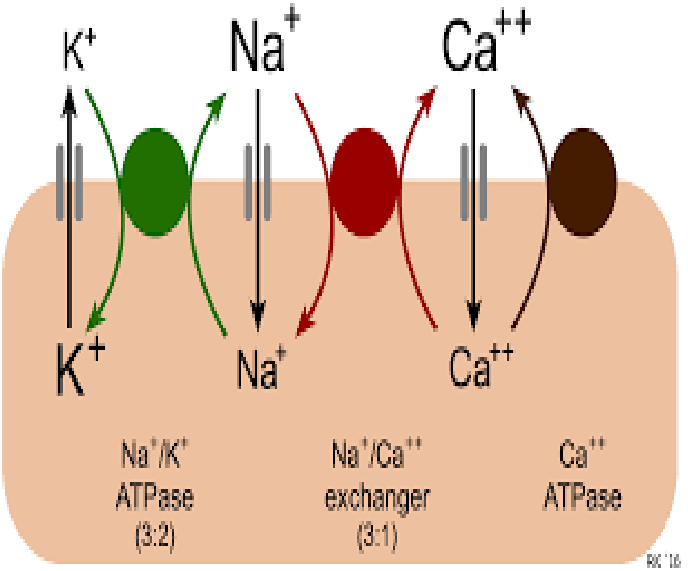
So, duration and amplitude of contraction depend on the availability of calcium.

- **Hormones**, **neurotransmitters**, and **drugs** that alter the inward Ca^{2+} current during the action potential plateau or that alter sarcoplasmic reticulum Ca^{2+} stores would be expected to change the amount of tension produced by myocardial cells.

Excitation-Contraction Coupling

- **Relaxation** occurs when the **intracellular Ca^{2+} concentration decreases to resting levels** by the following mechanisms:

1. Ca^{2+} is re-uptaken in the **sarcoplasmic reticulum** by the action of the **Ca^{2+} ATPase pump**.
2. Ca^{2+}, which entered the cell during the plateau of tl is extruded from the cell by **sarcolemmal**:
   - **Ca^{2+} ATPase pump** (an example of primary active
   - **Ca^{2+}-Na^{+} exchanger** (an example of secondary ac



Excitation-Contraction coupling (Quiz)

What is the correct order of the following events:

1. Ca^{2+} binding to troponin C.
2. Tension increase
3. Ca^{2+} release from sarcoplasmic reticulum
4. Ventricular action potential
5. Ca^{2+} reuptake by sarcoplasmic reticulum

4, 3, 1, 2, 5

Factors affecting Contraction

Positive inotropic agents: agents that ***increase*** contractility by increasing intracellular Ca^{2+} availability.

Negative inotropic agents: agents that ***decrease*** contractility by decreasing intracellular Ca^{2+} availability.

- **Preload**
- **Afterload**
- **Heart Rate**
- **Nervous (ANS)**
- **Hormones**
- **Ions**
- **Drugs**

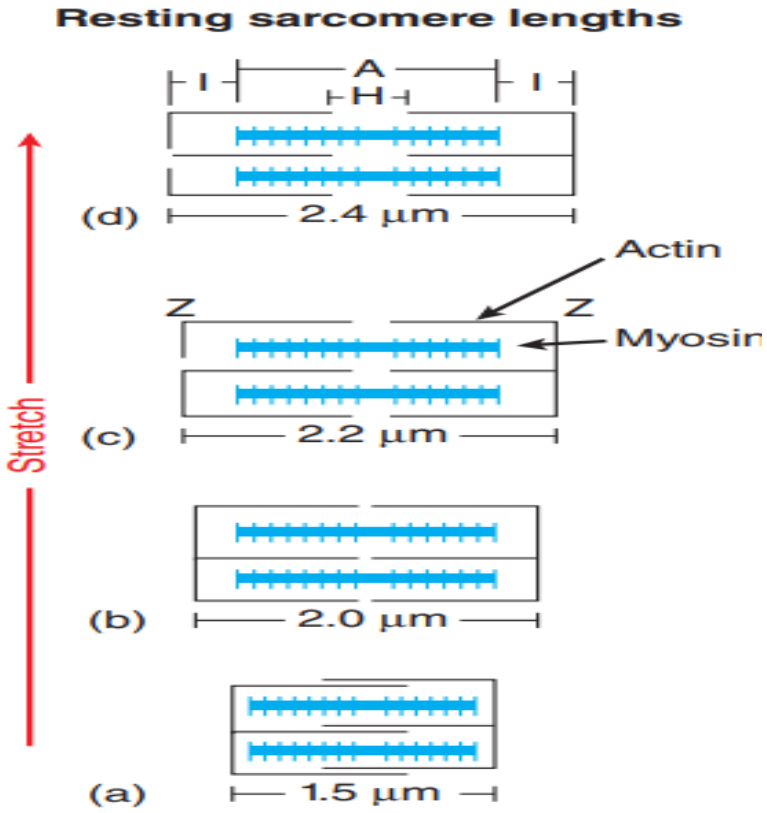
Factors affecting Contraction

Effect of Preload on Contraction (Length-tension relationship)

- **Definition:** The maximal tension that can be developed by a myocardial cell depends on its resting length.

The preload of the cardiac muscle is the venous return.

- **Physiologic basis**: The degree of overlap of thick and thin filaments and the number of possible sites for cross-bridge formation. In myocardial cells, maximal tension development occurs at sarcomere length of



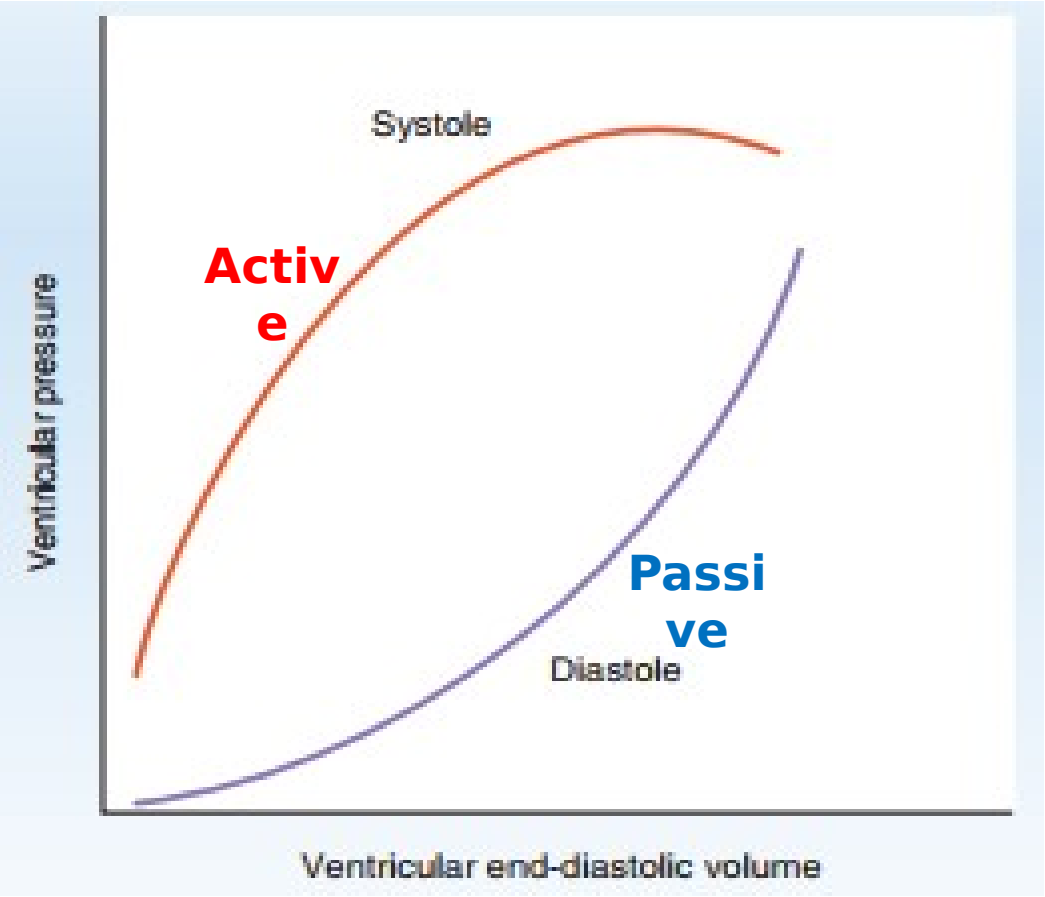
Factors affecting Contraction

Effect of Preload on Contraction

(Length-tension relationship)

Upper Curve: Frank-Starling relatinoship

Lower Curve



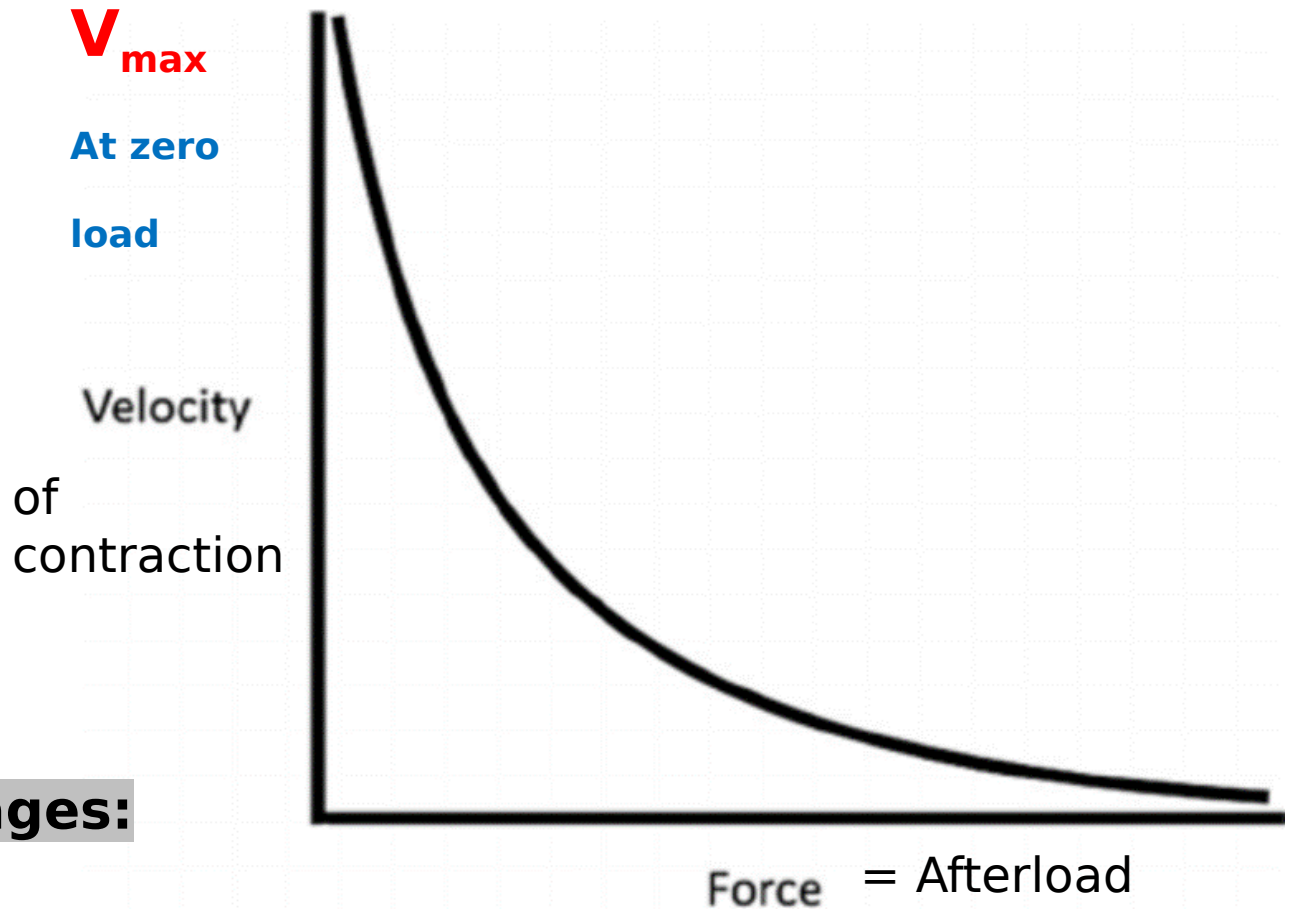
Factors affecting Contraction

Effect of Afterload on Contraction

(Force-Velocity relationship)

The **afterload** for the left ventricle is aortic pressure (for the right ventricle is pulmonary pressure).

The ***velocity*** of shortening of cardiac muscle is maximal when afterload is zero, and velocity of shortening



As cardiac muscle contracts against an afterload, its contraction occurs in 2 stages:

- **Isometric contraction**
- **Isotonic contraction**

Factors affecting Contraction

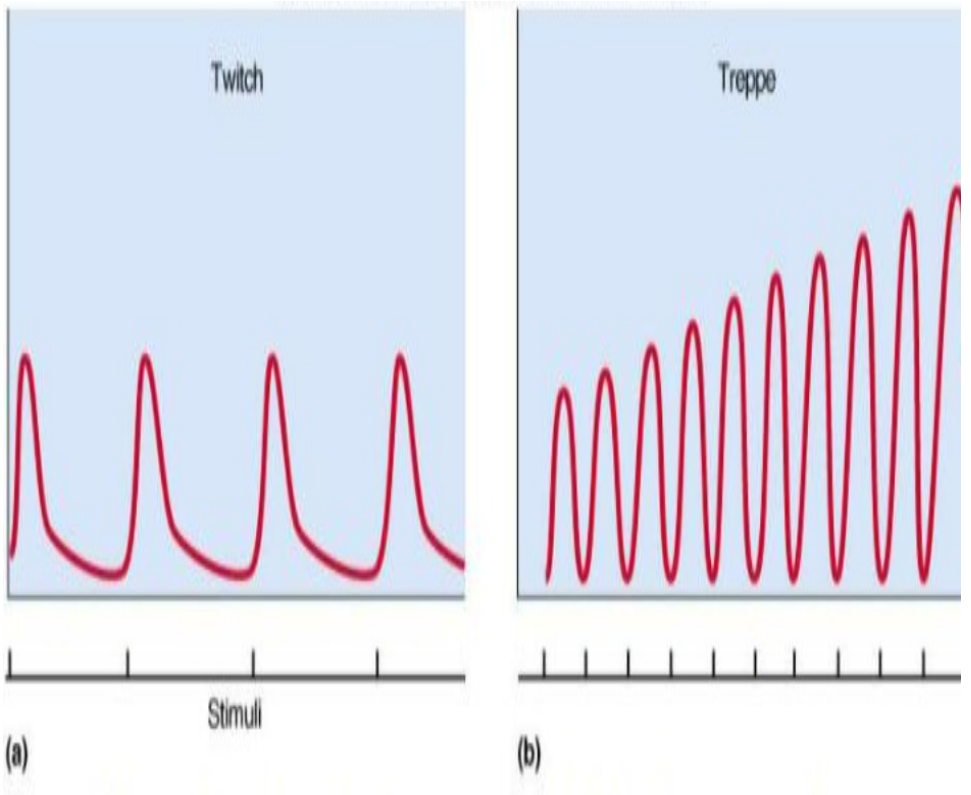
Effect of Heart Rate on Contraction (Force-Frequency relationship)

- Changes in heart rate produce changes in contractility (i.e. when the heart rate increases, contractility increases; when the heart rate decreases, contractility decreases).

Mechanism: as contractility correlates directly with intracellular Ca^{2+} concentration during excitation-contraction coupling, **When heart rate increases,**

(1) there are **more action potentials per unit time** and an increase in the total amount of trigger Ca^{2+} that enters the cell during the plateau phases of the action potentials.

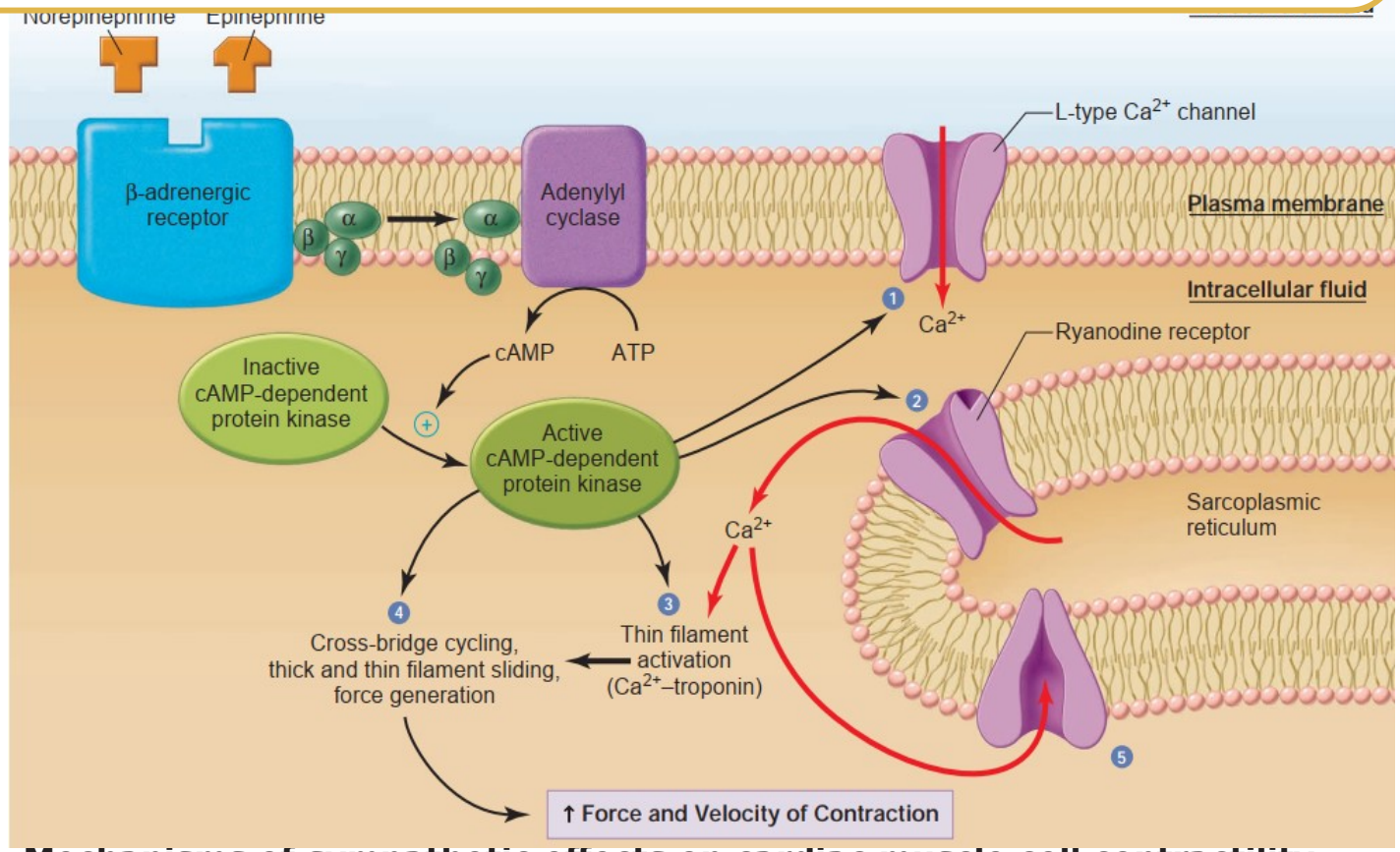
(2) there is greater influx of Ca^{2+} into the cell during the action potentials, the **sarcoplasmic reticulum accumulates more Ca^{2+}** for subsequent release (i.e., increased stored Ca^{2+}).



Effect of Autonomic Nervous System on Contraction

Sympathetic

- Positive Inotropic Effect
- Catecholamines
- Atria and ventricles
- β1 receptors
- Gs
- increases cAMP
- Activation of cAMP dependent protein Kinases
- More activity of sarcolemmal Ca^{2+} channel and



Mechanisms of sympathetic effects on cardiac muscle cell contractility

Factors affecting Contraction

Effect of Autonomic Nervous System on Contraction

Parasympathetic

- Negative Inotropic Effect
- Acetylcholine
- **Atria**
- Muscarinic (M2) receptors
- Gi
- Decreases cAMP
- Inactivation of cAMP dependent protein Kinases
- Less activity of sarcolemmal Ca^{2+} channel and sarcoplasmic Ca^{2+} ATPase

Factors affecting Contraction

Effect of Hormones on Contraction

Hormones with positive inotropic effect:

- **Catecholamines, glucagon** (by increasing cAMP)
- **Thyroid hormone** (by increasing ATPase activity & increase sensitivity to catecholamines)

Factors affecting Contraction

Effect of Ions on Contraction

- **Sodium:**

Hypernatremia (increased extracellular sodium) has **negative inotropic** effect. As hypernatremia favors Na^+ influx and Ca^{2+} efflux through the Na^+-Ca^{2+} exchanger, thus decreasing intracellular Ca^{2+} level, so decreasing force of contraction.

Hyponatremia (decreased extracellular sodium) has an opposite effect.

Factors affecting Contraction

Effect of Ions on Contraction

- **Calcium:**

Hypercalcemia (increased extracellular calcium) has **positive inotropic** effect and may **stop the heart during systole** (Ca^{2+} rigor) (**Spastic contraction**). As the trigger Ca^{2+} influx increases, it increases sarcoplasmic Ca^{2+} release (CICR), so increasing the force of contraction.

Hypocalcemia (decreased extracellular calcium) has an opposite effe

Hypercalcemia:
1- decreases excitability
2- increases contractility

Factors affecting Contraction

Effect of Ions on Contraction

- **Potassium:**

Hyperkalemia (increased extracellular potassium) has **negative inotropic** effect and may **stop the heart during diastole (Flaccid or dilated heart)**. As the extra cellular K^+ concentration increases, the K^+ cannot outflux from the myocardial cell, So, the negativity of the membrane potential of the muscle fibers decreases, reducing the amplitude of action potential, decreasing Ca^{2+} influx, and in turn decreasing Ca^{2+} release from sarcoplasmic reticulum, so decreasing force of contraction.

Hypokalemia (ssium) has an opposite effect.

Hyperkalemia:
1- increases excitability
2- decreases

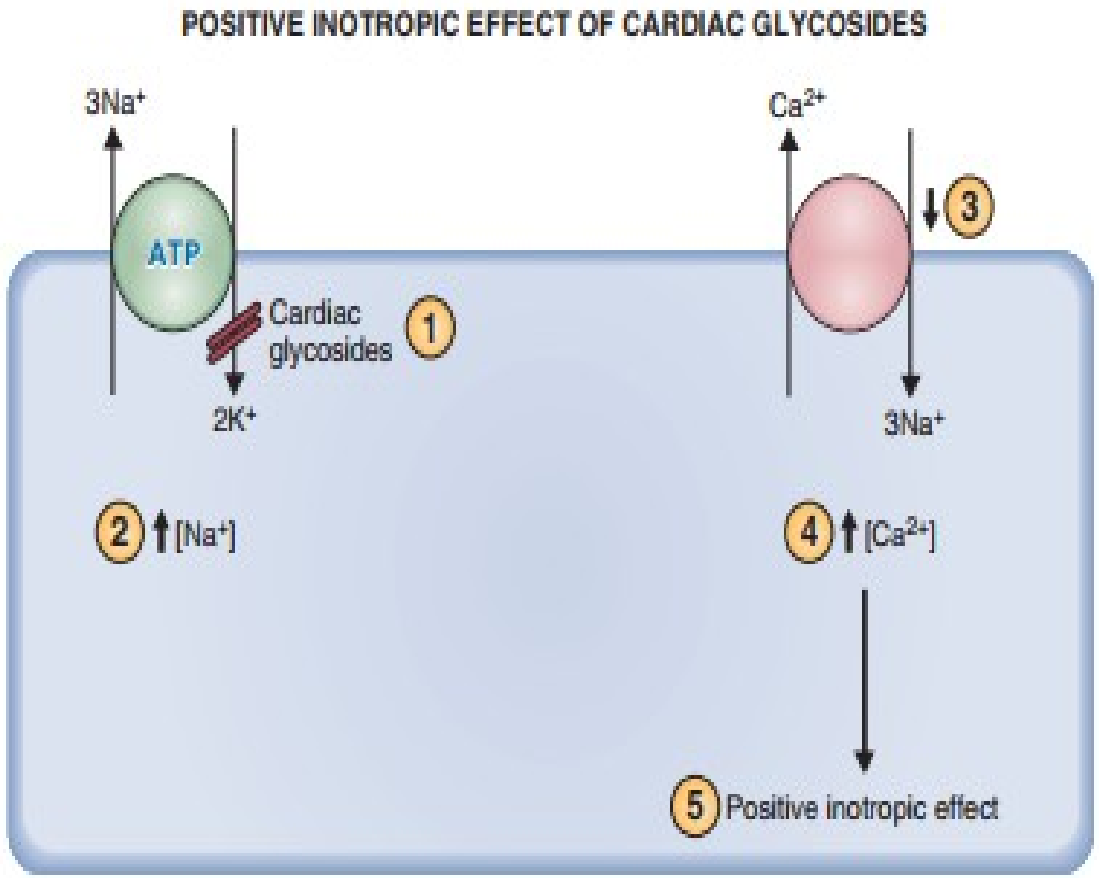
Factors affecting Contraction

Effect of Drugs on Contraction

Cardiac glycosides

Digitalis (digoxin, digitoxin and ouabain)

Used in the treatment of ***congestive heart failure***



Calcium channel blockers

Used in the treatment of ***Arrythmia, hypertension***

Factors affecting cardiac contractility (Quiz)

Which of the following produce(s) an increase in contractility:

1. Decreased heart rate
2. Hypercalcemia
3. Hyperkalemia
4. Digitalis
5. At sarcomere length > 2.2 µm

2, 4

Summary

- Excitation-contraction coupling in myocardial cells is similar to that in skeletal muscle. In myocardial cells, however, Ca^{2+} entering the cell during the plateau of the action potential serves as a trigger for the release of more Ca^{2+} from the sarcoplasmic reticulum.

- Intracellular [Ca^{2+}] determines the degree of inotropism, with positive inotropic agents increasing intracellular [Ca^{2+}] and contractility.

- Factors affecting contractility: Preload (venous return), Afterload (arterial pressure), Heart Rate, Autonomic Nervous System, Hormones (catecholamines, thyroxin and glucagon), ions (Ca^{2+}, K^{+}) and drugs (digitalis, Ca^{2+} channel blockers).

- Myocardial cells and the myocardium exhibit a length-tension relationship based on the degree of overlap of contractile elements (Frank-Starling law).

SUGGESTED TEXTBOOKS

1. Linda Costanzo from page 144 to 149